...TENT COOPERATION TREA. (

PCT	From the INTERNATIONAL BUREAU				
NOTIFICATION RELATING TO PRIORITY CLAIM					
(PCT Rules 26bis.1 and 26bis.2 and Administrative Instructions, Sections 402 and 409)	NOVO NORDISK A/S Enzyme Business Patents Novo Allé DK-2880 Bagsvaerd DANEMARK				
Date of mailing (day/month/year) 19 December 2000 (19.12.00)					
Applicant's or agent's file reference 6001.204-WO	IMPORTANT NOTIFICATION				
International application No. PCT/DK00/00460	International filing date (day/month/year) 21 August 2000 (21.08.00)				
Applicant					
NOVO NORDISK A/S et al					
The applicant is hereby notified of the following in respect of the	e priority claim(s) made in the international application.				
Correction of priority claim. In accordance with the applic the following priority claim has been corrected to read as	ant's notice received on: , follows:				
even though the indication of the number of the earlied even though the following indication in the priority claim the priority document:	er application is missing. aim is not the same as the corresponding indication appearing				
2. X Addition of priority claim. In accordance with the applicar the following priority claim has been added:					
US 01 September 1999 (01.09.99) 60/151,847 even though the indication of the number of the earlier application is missing.					
	aim is not the same as the corresponding indication appearing				
3. As a result of the correction and/or addition of (a) priority	claim(s) under items 1 and/or 2, the (earliest) priority date is:				
The applicant's notice was received after the expiration. The applicant's notice failed to correct the priority clather the applicant may, before the technical preparations for payment of a fee, request the International Bureau to public concerning the priority claim. See Rule 26bis.2(c) and the	im so as to comply with the requirements of Rule 4.10. international publication have been completed and subject to the blish, together with the international application, information PCT Applicant's Guide, Volume I, Annex B2(IB).				
 In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s): 6. A copy of this notification has been sent to the receiving Office and X to the International Searching Authority (where the international search report has not yet been issued). X the designated Offices (which have already been notified of the receipt of the record copy). 					
The International Bureau of WIPO	Authorized officer				
34, chemin des Colombettes 1211 Geneva 20. Switzerland	Jean-Marie McAdams				

Telephone No. (41-22) 338.83.38

Facsimile No. (41-22) 740.14.35

International application No.

PCT/DK 00/00460 A. CLASSIFICATION OF SUBJECT MATTER IPC7: C12P 19/18, C12N 9/26 // A23L 1/09 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC7: C12P, C08B, C12N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SE,DK,FI,NO classes as above Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Category* Citation of document, with indication, where appropriate, of the relevant passages P,X US 5958739 A1 (COLIN MITCHINSON ET AL), 1-27 28 Sept 1999 (28.09.99), column 1,2,3 P,X WO 9943793 A1 (NOVO NORDISK A/S), 2 Sept 1999 1-27 (02.09.99), & Geneseq database accession no. Y31731 100% identity in 719 aa overlap P,X WO 9943794 A1 (NOVO NORDISK A/S), 2 Sept 1999 1-27 (02.09.99), & geneseq database accession no. Y30621 100% identity in 719 aa overlap X EP 0120693 A1 (NOVO NORDISK A/S), 3 October 1984 1-27 (03.10.84), see page 13 and table 1 Χİ Further documents are listed in the continuation of Box C. See patent family annex. Special categories of cited documents: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international "X" document of particular relevance: the claimed invention cannot be filing date considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other document published prior to the international filing date but later than "&" document member of the same patent family the priority date claimed Date of the actual completion of the international search Date of mailing f the international search report 1 1 -01- 2001 <u> 2 January 2001</u> Name and mailing address of the ISA/ Authorized officer Sw dish Patent Offic Box 5055, S-102 42 STOCKHOLM Yvonne Siösteen/Eö

Telephone No. +46 8 782 25 00

Facsimile No. +46 8 666 02 86

International application No. PCT/DK 00/00460

	PCI/UK	00/00460
C (Continu	ation). DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passag	es Relevant to claim No.
x	WO 9510627 A1 (NOVO NORDISK A/S), 20 April 1995 (20.04.95), examples 1,2	1-27
	· 	
x	Swissprot database accession no. P19531, 01 feb 1991, 97.9% identity in 721 aa overlap & FEMS Microbiology Letters 56, Diderichsen 1988, pages 53-60	1-27
		
Y	US 5763385 A (RICHARD R. BOTT ET AL), 9 June 1998 (09.06.98), columns 1, 12	1-27
Y	US 4626288 A (PETER T. TRZASKO ET AL), 2 December 1986 (02.12.86), examples	1-27
		
A	WO 9100353 A2 (GIST-BROCADES N.V.), 10 January 1991 (10.01.91), pages 37-39	1-27
ı		
i		
		Ì
1		

International application No. PCT/DK00/00460

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This inter	national search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. 🔀	Claims Nos.: 1, 2 and 15 partially because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically: see next sheet
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
1.	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2 🗆	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



International application No. PCT/DK00/00460

Present claims 1, 2 and 15 are constructed in such a complex way and being so broad and speculative that it is not possible to carry out a meaningful search. See Art 17(2)(a).

Claims 1,2 and 15 fails to characterize the used variants in a way which is clear and concise. The expression has at least 70% identity in position 1-686 of SEQ ID NO:1" combined with ph optimum at 3.5-7 do not define the disired characteristics and properties of the enzyme in a definite way. The claims so lack support within the meaning of Article 6 PCT.

The search has mainly been carried out for a method using the maltogenic amylase having the amino acid 1-686 shown in SEQ ID NO:1 or for its mutated thermostable variant.

Form PCT/ISA/210 (extra sheet) (July1998)

Information on patent family members

04/12/00

International application No.
PCT/DK 00/00460

Patent document Publication cited in search report date			Patent family member(s)	Publication date		
US	5958739	A1	28/09/99	UA	6255796 A	24/12/96
	••••		20, 02, 02	BR	9608647 A	04/05/99
				EP	0832250 A	01/04/98
				JP	11506941 T	22/06/99
WO	9943793	A1	02/09/99	AU	2512899 A	15/09/99
				AU	2512999 A	15/09/99
				BR	9908281 A	31/10/00
				WO	9943794 A	02/09/99
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				EP	0927259 A	07/07/99
				JP	2000509995 T	08/08/00
				WO	9743424 A	20/11/97

Information on patent family members

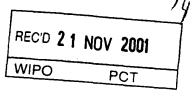
04/12/00

International application No. PCT/DK 00/00460

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				SE	0410498 T3		
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PATENT COOPERATION TRATY





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 6001.204-WO			FOR FURTHER AC	CTION		cation of Transmittal of International y Examination Report (Form PCT/IPE	A/416)
			International filing data	dov/month		Priority date (day/month/year)	
PCT/DK			International filing date (iii) 21/08/2000	uay/monu	vyear)	01/09/1999	
						01/03/1999	
C12P19		ent Classification (IPC) or na	tional classification and IPC	j			
Applicant							
Applicant	/8 AFT C	2.4/0.54.51		•			
NOVOZ	YIVIES	S A/S et al.					
		ational preliminary exami smitted to the applicant a		prepared	by this Inte	ernational Preliminary Examining	Authority
2. This	REPC	PRT consists of a total of	9 sheets, including this	cover sl	neet.		
t	een a		is for this report and/or	sheets c	ontaining re	on, claims and/or drawings which ectifications made before this Autl ne PCT).	
Thes	e ann	exes consist of a total of	sheets.				
							
3. This	eport	contains indications rela	ting to the following iter	ns:			
1		Basis of the report					
H	_	Priority					
111		•	pinion with regard to no	velty, inv	entive step	and industrial applicability	
IV		Lack of unity of invention	·	3 .	•	,	
٧	⊠	· ·	nder Article 35(2) with re		novelty, inve	entive step or industrial applicabil	ity;
VI		Certain documents cité	ed				
VII	\boxtimes	Certain defects in the in	ternational application				
VIII	\boxtimes	Certain observations or	the international applic	ation			
Date of submission of the demand Date of completion of this report							
10/02/2001				19.11.20	001		
	,	g address of the international ining authority:		Authoriz	ed officer	<u>/</u> \$	CONSONES MICHIGAN
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d				Vogt, T		Stand Cart	
		+49 89 2399 - 4465	Spirite S	Telepho	ne No. +49 89	9 2399 8477	WIS SOURCE SHARE AND

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00460

I.	Bas	is f the report			
1. With regard to the elements of the international application (Replacement sheets which have been the receiving Office in response to an invitation under Article 14 are referred to in this report as "orig and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)). Description, pages:					
	1-55	as originally filed			
	Clai	ms, No.:			
	1-27	as originally filed			
	Seq	uence listing part of the description, pages:			
	_	, as originally filed			
2.	With lang	regard to the language , all the elements marked above were available or furnished to this Authority in the luage in which the international application was filed, unless otherwise indicated under this item.			
	The	se elements were available or furnished to this Authority in the following language: , which is:			
		the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).			
		the language of publication of the international application (under Rule 48.3(b)).			
		the language of a translation furnished for the purposes of international preliminary examination (under Rul 55.2 and/or 55.3).			
3.	With	n regard to any nucleotide and/or amino acid sequence disclosed in the international application, the rnational preliminary examination was carried out on the basis of the sequence listing:			
	×	contained in the international application in written form.			
		filed together with the international application in computer readable form.			
		furnished subsequently to this Authority in written form.			
		furnished subsequently to this Authority in computer readable form.			
		The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.			
		The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.			
4.	The	amendments have resulted in the cancellation of:			
		the description, pages:			

☐ the claims,

☐ the drawings,

Nos.:

sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00460

5.		This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
		(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6.	Add	litional observations, if necessary:
II.	Pric	prity
1.	Ø	This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
		□ copy of the earlier application whose priority has been claimed.
		☐ translation of the earlier application whose priority has been claimed.
2.		This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.
	Thu date	s for the purposes of this report, the international filing date indicated above is considered to be the relevant e.
3.	Ado	litional observations, if necessary:
		n-establishment of opinion with regard to novelty, inventive step and industrial applicability
1.		questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- ious), or to be industrially applicable have not been examined in respect of:
		the entire international application.
	Ø	claims Nos. 1, 2, 15.
be	caus	e:
		the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (<i>specify</i>):
		the description, claims or drawings (<i>indicate particular elements below</i>) or said claims Nos. are so unclear that no meaningful opinion could be formed (<i>specify</i>):
		the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
	×	no international search report has been established for the said claims Nos. 1, 2, 15.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00460

2.	A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide
	and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative
	Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes:

Claims 1-27

No:

Claims

Inventive step (IS)

Yes:

Claims 1-16 (part)

No:

Claims 1-16 (part), 17-27

Industrial applicability (IA)

Yes:

Claims 1-27

No: Claims

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

Priority (Art. 8 PCT). 11

On the question whether D1- D3 constitute prior art according to Chapter II PCT proceedings depends on the validity of the priority claim. The analysis of the priority rights will however only be performed in the regional European proceedings to come.

Whether the contents of said documents is relevant for the assessment of inventive step will also be decided after the assessment of the priority rights.

Ш No opinion.

See international search report.

Reasoned Statement (Rule 66(2) PCT). ٧

Subject matter of the present application.

The provision of two methods for the preparation of an enzymatically modified starch derivative, wherein starch is digested by an amylase, characterized in that the starch is chemically derivatised either prior (claim 1) or after (claim 2) digestion and that said amylase is depicted by, or is at least 70% homologous to, Seq. ID No:1(also known under the name: Novamyl[SPEC0429]).

Cited prior art documents (Rule 64(1) PCT).

EP-A-0832250 (01.04.1998) US-A-5958739. (28.09.1999) D1: =>

WO-A1-9943793. D2:

WO-A1-9943794. D3:

EP-A1-0120693. D4:

WO-A1-9510627. D5:

Diderichsen & Christiansen (1988) FEMS MICROBIOL. LETT. 56, 53-60. D6:

D7: US-A-5763385.

US-A-4626288. D8:

WO-A-29100353. D9:

Added by the examiner:

(cited in the description). US-A-4977252. D10:

(cited in the description). D11: US-A-2661349.

D1 relates to the improvement of the enzymatic characteristics of α -amylases by genetic engineering. The aim of D1 is to modify the pH range, and the oxidative- and thermal- stability of amylases by single or multiple AA substitutions. As an example D1 mentions the α -amylase obtained from Bacillus stearothermophilus (cf. p. 5). On p. 9 it discloses that there is sequence homology between the different forms of endoamylases, as an example D1 states that the α -amylases obtained from B. stearothermophilus has a 66% homology to that obtained from B. Licheniformis.

D2-D6 all disclose the parental enzyme Novamyl (Seq ID No: 1) of the present application. In particular D3 appears to be of interest as it discloses some of the Novamyl analogs also used in the present application (see for instance variants F188L+D261G+T288P, which is used in most of the examples in the present application, and T142A+N327S+K425E+K520R+N595I). All documents D2-D6 disclose the use of Novamyl to digest starch, but not starch derivatives.

D7 relates to the modification of the enzymatic properties of α -amylases by genetic engineering. D7 mainly focuses on the Ca2+ binding site.

D8 mentions the modification of starches by chemical derivatisation with hydrophilic or hydrophobic groups. D8 does not mention the possibility of a subsequent digestion with an amylase.

D9 discloses the modification of microbial amylases by genetic engineering to improve the thermal-, acid- and/or alkali-stability. D9 anticipates the modification of α -amylase produced by Bacillus stearothermophilus (cf. claims), but exemplifies its invention with α-amylase obtained from Bacillus licheniformis.

D10 relates to the preparation of modified starch derivatives by first chemically derivatising the starch and subsequently digesting the starch derivate with an exoamylase. D10 thus differs from the present application in that a different amylase is used to digest the starch derivative.

Novelty (Art. 33(2) PCT).

The subject matter of the present application meets the requirements of novelty.

Inventive step (Art. 33(3) PCT).

Novamyl is known as a maltogenic endo α -amylase (cf. D2-D6), the derivatisation of starch is also known (cf. D8, D10), the subsequent digestion with an amylase is also known (cf. D10). Furthermore it is known that one can modify the enzymatic properties of amylases by genetic engineering (cf. D1, D7 and D9). So the invention must be found in the use of Novamyl (or an analog derived therefrom) in the digestion of starch derivatives. As the applicant already indicates: 'there appears to be no prior art that discloses the use of an endo α -amylase for the digestion of derivatised starch' (p. 7, I. 28-31).

It appears, however to be a small step for a skilled artisan to exchange one amylase for another, particularly if one can anticipate the advantage of such an exchange in advance. Hence, claim 1 lacks an inventive step insofar as it relates to Novamyl. With regard to the variants of Novamyl the applicant is referred to the discussion in the written opinion of the copending application PCT/DK00/00460. In short, the preparation of the variants lacks an inventive step over a comparison of the crystal structure of Novamyl (Dauter et al. (06.1999) Biochemistry 38, 8385) with that of CGTase (Lawson et al. (1994) JMB (1994) 236, 590) and the identification of relevant site within said CGTase, extended with the further work published by the groups of Prof. Dijkstra and Prof. Dijkhuizen on the relation between the structure and activity of CGTase (by way of example WO-A-9633267, Penninga et al. (1995) Biochemistry 34, 3368; Knegtel et al. (1995) JBC 270, 29256; Knegtel et al. (1996) JMB 256, 611; Wind et al. (1998) Eur. J. Biochem. 253, 598; Wind et al. (1998), JBC 273, 5771; a copy of which will be annexed to this communication. Based on the above the examiner is of the opinion that the general wording of claim 1 with respect to the variant of Novamyl does not comprise an inventive step. The examiner would be willing to accept the presence of an inventive step for some of the specific variants of Novamyl disclosed in the description, insofar as they have not been previously disclosed by D2 or D3.

The attention of the applicant is further directed to point VIII below with regard to the broad wording of claim 1.

Claim 2 relates to chemical derivatisation of digested starch. This claim belongs in the copending application PCT/DK00/00460, which relates to the digestion of underivatised starch by homologous of Novamyl. This claim lacks an inventive step, because it is an obvious extension of a known process. The advantage of the chemical derivatisation of

the digested product can be anticipated in advance.

The same argumentation also applies for claim 15. It should be noted that Novamyl itself does not appear to be excluded from said claim.

Since the claims 3-14 and 16 do not contain any features not already known from the prior art they cannot confer an inventive step to the subject matter insofar as Novamyl is concerned.

Claim 17 relates to a product obtained by the processes of any of claims 1-14. Since the use of Novamyl for the digestion of 'derivatised' starch is not considered to be inventive and the analogs thereof (in fact any endo-nuclease) are expected to produce the same final product, also the product of the process cannot be considered to comprise an inventive step. Following this line of argumentation also the uses (claims 18-27) of the product cannot be considered to comprise an inventive step.

Industrial applicability (Art. 33(4) PCT).

The amylase analogs of the present application have improved enzymatic properties. The products obtained by the enzymatic digestion of starch using these amylase analogs can be used in various products.

Hence, the subject matter of the present application meets the requirements of industrial applicability.

Remarks related to the description (Art. 5 PCT).

To meet the requirements of Rule 5 PCT the applicant is requested to identify D1 and D5-D9

VIII Clarity and support of the claims (Art. 6 PCT).

Claims 1, 2 and 15 relate to amylases having a 70% identity with the amino acid sequence of the protein depicted by Seq ID No:1. The protein of Seq. ID No: 1 contains 686 AA. The largest modification to this sequence was a 6 amino acid substitution or deletion. This is far above 70% identity (>99%).

Hence, there is no support in the description for the broad wording of claim 1 and the

wording is unclear (Art. 6 PCT).

The term 'deriving' in claim 2 (Ia) and p. 5, I. 7 should read 'derivatising'.

Claims 6-8 and 10 are written as results to be achieved. The claims should generally be written in terms of the technical features how these results are to be achieved. In this case however the wording is allowable, because it does not constitute the 'real' invention of the application, and the methods via which these results should be obtained are generally known.

The word 'herein' in claim 11 should read 'wherein'.

The word 'modified' should be inserted in claim 24 between enzymatically and starch.

Claim 25 relates to product claim, wherein one of the constituents is defined as 'a product obtained by a process'. Such a formulation renders the scope of the claims unclear.

The applicant is informed that the use of the term 'preferably' in claims is not considered to be restrictive on the scope of said claims.